R E M A R K S

Priority Claim under 35 USC 119

Item no. 5 at the bottom of page 2 of the August 20, 2008 Office Action indicated receipt of the English-language translations of applicant's priority documents. However, item no. 12 on page 1 of the August 20, 2008 Office Action did not have any indication regarding applicant's claim for priority under 35 USC 112 or receipt of the certified copies of the priority documents.

The Examiner is respectfully requested to acknowledge applicant's claim for priority under 35 USC 119 and receipt of the certified copies of the priority documents which were received by the USPTO (see the NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.495 dated October 10, 2006).

Information Disclosure Statement

In reply to item no. 7 on page 3 of the August 20, 2008 Office Action, enclosed herewith is a copy of the English-

language translation of the Written Opinion of the International Searching Authority (Form PCT/ISA/237) for PCT/JP2004/016715.

Presently Claimed Invention

The presently claimed invention is directed to an oligonucleotide comprising:

(a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides;

(b) a nucleotide complementary to the reference nucleotide of a target gene at the 3'-end position thereof; and

(c) nucleotides complementary to a nucleotide sequence of the target gene in other positions,

or a salt thereof (see applicant's claim 1).

The presently claimed invention also relates to an oligonucleotide comprising:

(a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides;

(b) a nucleotide complementary to the mutant nucleotide of a target gene at the 3'-end position thereof and

(c) nucleotides complementary to a nucleotide sequence of the target gene in other positions,

or a salt thereof (see applicant's claim 2).

The presently claimed invention further pertains to an oligonucleotide comprising:

(a) a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to the reference nucleotide of a target gene;

(b) a nucleotide which is the second nucleotide from the 3'-end of the oliginucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, the second nucleotide is a nucleotide that is not complementary to the nucleotide of a reference gene;

(c) a region of the nucleotides complementary to a region of the target gene in other positions; and

(d) a nucleotide which is the third nucleotide from the 3'-end of the oligonucleotide is a 2'-O,4'-C-ethylene nucleotide (ENA) unit, and the other nucleotides are natural nucleotides,

or a salt thereof (see applicant's claim 3).

The presently claimed invention is also directed to an oligonucleotide comprising:

(a) a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to the mutant nucleotide of a target gene;

(b) a nucleotide which is the second nucleotide from the 3'-end of the nucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, the second nucleotide is a nucleotide that is not complementary to the nucleotide of a reference gene;

(c) a region of the nucleotides complementary to a region of the target gene in the other positions; and

(d) a nucleotide which is the third nucleotide from the 3'-end of the oligonucleotide is a 2'-O,4'-C-ethylene nucleotide (ENA) unit, and the other nucleotides are natural nucleotides,

or a salt thereof (see applicant's claim 4).

The gist of the presently claimed invention is that the third nucleotide form the 3'-end of the oligonucleotide is an ENA unit.

Rejections under 35 USC 103

In the August 20, 2008 Office Action, the Examiner maintained each of the following three obviousness rejections under 35 USC 103 that were set forth in the previous Office Action of February 19, 2008:

(1) Claims 1 to 5, 23, 29 and 41 were rejected under 35 USC 103 as being unpatentable over Latorra et al., Human Mutations, (2003), 22, 79-85 (hereinafter referred to as "Latorra et al.") and Koizumi et al., Nucleic Acids Research, (2003), 13, No. 12, 3267-3273 (hereinafter referred to as "Koizumi et al."). This rejection was maintained for the reasons set forth in item no. 11 on pages 4 to 5 of the August 20, 2008 Office Action.

(2) Claims 12 to 19 and 52 to 54 were rejected under 35 USC 103 as being unpatentable over Latorra et al., Koizumi et al. and Weston et al. (USP 6,391,593). This rejection was maintained for the reasons stated in item no. 12 on pages 5 and 6 of the August 20, 2008 Office Action.

(3) Claims 20 to 22, 24 to 28, 30 to 40 and 42 to 43 were rejected under 35 USC 103 as being unpatentable over Latorra et al., Koizumi et al. and Stanton et al. (USC 2001/0034023). This

rejection was maintained for the reasons indicated in item no. 13 on page 6 of the August 20, 2008 Office Action.

At the middle of page 5 of the August 20, 2008 Office Action, reference was made to the legend of Table 1 on page 81 of Lattora et al., wherein the following was stated:

> "A total of 16 forward DNA and 3' LNA primers were designed for each of three pUC19 targets, and included match and the three other possible mismatch combinations at the last four positions of each 3' end."

The following position was taken in the last paragraph on page 4 and the first sentence on page 5 of the August 20, 2008 Office Action:

> "...Latorra et al. clearly teach the LNA is placed 'at the last four positions of each 3'-end.' Furthermore, this is done for each of the three forward primers in sets 1-3 as given in the Table 1. The last four positions of each of these primers include the third position from their 3'-end. Each of these three forward primers has a four base 3'-end in which the four bases are T, C, G and A in different orders. Primers were then made where each of these bases was substituted with an LNA complementary match to corresponding template base and with each of the remaining three LNA mismatches (non-complementary bases, see Figure 2 and its legend). Thus Latorra et al. not only designed 16 such LNA primers for each of the

> three forward primers but made these primers as evidenced by Figure 2."
>
> "Thus as Latorra et al. teach an LNA unit which is the third nucleotide from the 3'-end. As given in the previous Office Action, Koizumi et al. teach ENA units and teach that ENA units can be substituted for LNA units. Thus, as also given previously, it would have been obvious to substitute the ENA units of Koizumi et al. for the LNA units of Latorra et al. to arrive at the claimed invention."

Applicant's Reply to the Rejections under 35 USC 103

It was admitted at the top of page 10 of the February 19, 2008 Office Action that Latorra et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit.

It was also admitted at the middle of page 10 of the February 19, 2008 Office Action that Koizumi et al. do not specifically teach an oligonucleotide comprising ENA units at the third position from the 3' end.

As discussed hereinbelow in detail, applicant respectfully submits the following:

(1) **Latorra et al. do not teach or suggest an oligonucleotide comprising a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the third nucleotide from the 3'-end of the oligonucleotide**, wherein the nucleotide at the 3'-end is defined

as the first nucleotide, and the other nucleotides are natural nucleotides, as recited in applicant's present claims.

(2) **Koizumi et al. do not teach or suggest the interchangeability of LNA** (as disclosed in Latorra et al.) **for ENA** (as recited in applicant's present claims).

Latorra et al.

It is repeatedly stated in Latorra et al. that a locked nucleic acid **(LNA) is at the 3' position**. In this regard, see the following excerpts from Latorra et al.:

Abstract, line 1 on page 79 of Latorra et al.:

"...locked nucleic acid (LNA) substitution at the 3' position...."

In the left column, lines 20 to 24 on page 80 of Latorra et al., the following is stated:

> "In this report we investigated the specificity and sensitivity of AS-PCR with primers containing **a single locked nucleic acid (LNA) base at the 3' terminal position (referred to as LNA primer).**" (emphasis added)

In the right column, lines 10 to 12 of Latorra et al., the following is stated:

> "Primer **3' terminal matches and mismatches** were used to interrogate plasmid and human genomic target sites." (emphasis added).

In the right column, lines 19 to 21 of Latorra et al., the following is stated:

> "LNA primers show very accurate mismatch discrimination in comparison with DNA primers at all **3' terminal positions** with the plasmid template." (emphasis added)

In the right column, lines 17 to 20 on page 81 of Latorra et al., the following is stated:

> "Matches DNA and LNA primers were designed for three target sequences in pUC19 having A, C, G or T **at the position corresponding to the 3' end**, along with all possible 3' mismatched primer (see Table 1 legend)." (emphasis added)

Submitted herewith is a DECLARATION UNDER 37 CFR 1.132 of Makoto KOIZUMI dated October 29, 2008 (referred to hereinafter as the KOIZUMI DECLARATION). The following is stated on page 5 of the KOIZUMI DECLARATION:

> "Latorra et al. made primers containing a LNA at the 3' terminal position and with all possible matched and mismatched base pairs at the 3' terminal position."

As noted above at the middle of page 4 of the August 20, 2008 Office Action, reliance was placed on the following statement in the legend of Table 1 on page 81 of Latorra et al., wherein the following is stated:

> "A total of 16 forward DNA and 3' LNA primers were designed for each of three pUC19 targets, and included match and the three other possible mismatch combinations at the last four positions of each 3' end."

The August 20, 2008 Office Action, however, neglected to refer to the remainder of the legend of Table 1 on page 81 of Latorra et al., wherein the following is stated:

> "The core sequence shown is the furthest perfect match to the right of the final base sequence. Three other matched forward primers (each ending with a different base) were made by staggering one base to the left from this core sequence and maintaining a constant length (18nt). Human CFTR primers **ending with 3' DNA and LNA** residue were designed for polymorphisms ...." (emphasis added)

It is respectfully submitted that the teaching of the legend for Table 1 in Latorra et al. was misinterpreted in the August 20, 2008 Office Action with respect to the position of the LNA.

Pages 6 to 10 of the KOIZUMI DECLARATION show possible sequences for LNA primers intended by legend for Table 1 of Latorra et al.

Using Forward Primer 1 as an example, the enclosed KOIZUMI DECLARATION provides examples of what was intended by the legend for Table 1 on page 81 of Latorra et al.

Sixteen primers, made of the same length at the Forward Primer 1, were made by a match and three possible mismatch combinations at the last four positions of the 3' end. These were made by altering only the bases at the 3' terminal position.

To obtain the 16 primers, a new primer was made as a copy of the previous primer, except for containing a new base at the 5' end and removing the base at the 3' terminal position (to maintain a constant length).

Another interpretation of the legend for Table 1 of Latorra et al. is as follows:

If the Forward Primer 1 in Latorra et al. is represented as follows:

5' end GCGGGCCTCTTCGCTATTACG 3'end
|
LNA

then possible mismatches and matches at the third position from the 3' end could be as follows:

```
5' end    GCGGGCCTCTTCGCTATTGCG      3'end
                                |
                               LNA                    or

5' end    GCGGGCCTCTTCGCTATTTCG      3'end
                                |
                               LNA
```

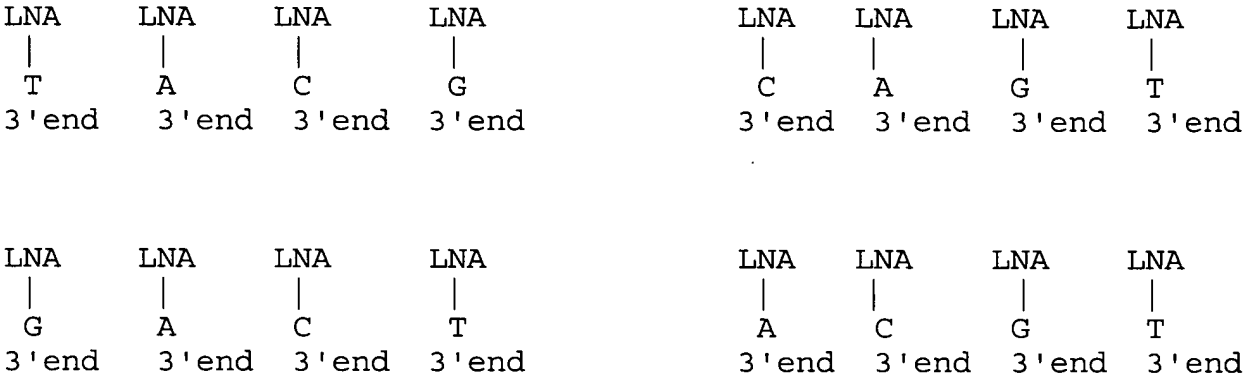
Contrary to the position taken in the last paragraph on page 4 of the August 20, 2008 Office Action, Latorra et al. do not teach the placement of LNA "at the last four positions of each 3' end." Latorra et al. teach that LNA is always at the 3' terminal end, regardless of the arrangement of the bases in the last four positions of the 3' terminal end.

The discussion in the legend for Table 1 of Latorra et al. regarding "match and the other three possible mismatch combinations at the last four positions of each 3' end" refer only to the bases, and do not refer to the position of the LNA (see the enclosed KOIZUMI DECLARATION).

As discussed above, pages 79 to 81 of Latorra et al. require that the LNA is always at the 3' end. The legend for Table 1 of Latorra et al. does not change this requirement.

The characterization of Figure 2 of Latorra et al. in the last two sentences on page 4 of the August 20, 2008 Office Action is submitted to be incorrect.

It is respectfully submitted that Figure 2 of Latorra et al. teaches the following:



The following is stated in the last paragraph on page 10 of the enclosed KOIZUMI DECLARATION:

> "As described above, a person of ordinary skill in the art would consider that Latorra et al. used these primers containing a LNA at the 3' terminal position and with all possible matched and mismatched base pairs at the 3' terminal position. Therefore, a person of ordinary skill in the art would not consider to place a LNA at the third position from the 3' end based on the disclosure of Latorra et al."

Koizumi et al.

The following is stated on pages 11 to 12 of the enclosed KOIZUMI DECLARATION:

It is respectfully submitted that a person of ordinary skill in the art would not consider to substitute the ENA units of Koizumi et al. for the LNA units of Latorra et al. for the following reasons:

ENA units are considered to be superior to LNA units in triplex formation as described in Koizumi et al. This means that triplex forming oligonucleotides (TFOs) containing ENA units can tightly bind to double-strand DNA to form triplexes compared to TFOs containing LNA units. In Koizumi et al., molecular interaction between double-strand DNA and modified oligonucleotides such as ENA and LNA is discussed.

Molecular interaction between double-strand DNA and TFO is described in Chapter 27, line 1 on page 487 of Applied Antisense Oligonucleotide Technology, (1998), edited by C.A. Stein and Arghur M. Krieg as follows:

> "Triple helix formation can be mediated by binding of selected oligonucleotides to homopurine regions of the duplex DNA. These triplex-forming oligonucleotides (TFO) bind specifically in the major groove of the DNA,

> forming hydrogen bonds with bases in purine-rich strand."

However, in the above-identified patent application, it is disclosed how DNA polymerase recognizes double-stranded DNA with a template and a primer and elongates a strand. It is a molecular interaction between a protein and a double-stranded DNA modified with ENA.

Molecular interaction between a protein and a double-stranded DNA is described in the Summary on page 345 of Nucleic Acids in Chemistry and Biology, (1990), edited by G. Michael Blackburn and Michael J. Gait as follows:

> "All nucleic acids have repeating polyanionic backbones, and so all proteins that bind to nucleic acids have strategically placed arginines and lysines that create an electrostatic field to neutralize the negative charge. To interact with B-DNA, the protein either (1) inserts an alpha-helix into the major groove, or (2) inserts a beta-sheet into the major groove, and form hydrogen-bonds from the side-chains to specific bases."

The disclosure in Koizumi et al. involving a molecular interaction between double-strand DNA and modified oligonucleotides such as ENA and LNA, is completely and qualitatively different from the above-identified application,

which concerns a molecular interaction between a protein and a double-strand DNA modified with ENA. Therefore, one of ordinary skill in the art would not consider substituting the ENA units of Koizumi et al. for the LNA units of Latorra et al.

Weston et al.

In item no. 24 on page 16 of the February 19, 2008 Office Action, the following position was taken:

"Weston et al. teach kits comprising oligonucleotides with LNA units, DNA polymerases and PCR buffers (see column 7, lines 41 to 51, and see claims 20 and 21)."

Weston et al. do not specify the position and number of LNA units in their probes. In contrast thereto, applicant's claims specify the position (the third position) and number (one) of an ENA unit (the third nucleotide from the 3'-end thereof is a 2'-,4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the first nucleotide).

In addition, Weston et al. disclose a kit which comprises a following pair of probes:

(a) first probe: comprising a portion complementary to the sequence of interest and capable of hybridizing

thereto, and a portion non-complementary to the sequence of interest;

(b) second probe: comprising a portion complementary to the sequence of interest and capable of hybridizing thereto, and a portion non-complementary to the sequence of interest, but complementary to that portion of the first probe which is non-complementary to the sequence of interest.

The structure of said pair of probes in Weston et al. is completely different from applicant's claims. It is therefore respectfully submitted that Weston et al. do not teach or suggest applicant's claimed kits.

Stanton et al.

It was admitted on page 17 of the February 19, 2008 Office Action that Latorra et al. and Koizumi et al. do not teach the features of applicant's claims 20 to 22, 24 to 28, 30 to 40 and 42 to 43.

In item no. 25 on page 17 of the February 19, 2008 Office Action, the following position was taken:

> "Stanton et al. teach oligonucleotide/primers for detecting drug metabolizing genes."

Stanton et al. do not teach or suggest an oligonucleotide as recited in applicant's claims (the third nucleotide from the 3'-end thereof is a 2'-O,4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the first nucleotide) for detecting drug metabolizing genes.

Summary

It is respectfully submitted that all the obviousness rejections are based on a misinterpretation of Latorra et al.

Latorra et al. teach nucleotides whose LNA nucleotide is fixed only at the 3' end. In contrast thereto, applicant's claims are directed to nucleotides whose ENA nucleotide unit is the third nucleotide from the 3'-end. The nucleotides recited in applicant's claims are thus completely different from the nucleotides disclosed in Latorra et al.

It is therefore respectfully submitted that one of ordinary skill in the art would not arrive at applicant's present claims in view of the disclosures of the references.

Withdrawal of each of the obviousness rejections is thus respectfully requested.

Rejoinder

If the claims of Group I are allowed, rejoinder and allowance of the claims of Group II are respectfully requested (see item no. 3 on pages 4 to 5 of the November 15, 2007 Office Action).

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted

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Enclosures:
(1) a copy of an English-language translation of the Written Opinion of the International Searching Authority (Form PCT/ISA/237) for PCT/JP2004/016715
(2) DECLARATION UNDER 37 CFR 1.132 of Dr. Makoto Koizumi dated October 29, 2008
(3) a copy of the cover page, the copyright page and page 487 of Applied Antisense Oligonucleotide Technology, (1998)
(4) a copy of the cover page, the copyright page and page 345 of Nucleic Acids in Chemistry and Biology, (1990)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY
(CHAPTER I OR CHAPTER II
OF THE PATENT COOPERATION TREATY)
(PCT Rules 44*bis*.3(c) and 72.2)

To:

OHNO, Akio
c/o SANKYO COMPANY, LIMITED, 2-58, Hiromachi
1-chome, Shinagawa-ku, Tokyo
1408710
JAPON

Date of mailing *(day/month/year)* 03 August 2006 (03.08.2006)	
Applicant's or agent's file reference sankyoFP0427	**IMPORTANT NOTIFICATION**
International application No. PCT/JP2004/016715	International filing date *(day/month/year)* 04 November 2004 (04.11.2004)
Applicant SANKYO COMPANY, LIMITED et al	

1. **Transmittal of the translation to the applicant.**

☑ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).

☐ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

2. **Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

None

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. **Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

知財部
06. 8. 21
受付

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yoshiko Kuwahara
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference sankyoFP0427	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2004/016715	International filing date *(day/month/year)* 04 November 2004 (04.11.2004)	Priority date *(day/month/year)* 07 November 2003 (07.11.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant SANKYO COMPANY, LIMITED		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 27 July 2006 (27.07.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference sankyoFP0427	Date of mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/016715	04.11.2004	07.11.2003

International Patent Classification (IPC) or both national classification and IPC

Applicant
SANKYO COMPANY, LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/016715

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☒ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/016715

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19	YES
	Claims		NO
Inventive step (IS)	Claims	1-19	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims		NO

2. Citations and explanations:

Document 1: Nucleic Acids Res. (2003-Jun), Vol. 31, No. 12, p. 3267-3273
Document 2: Bioorg. Med. Chem. Lett. (2002), Vol. 12, No.1, p. 73-76
Document 3: Kosei Rodosho Seishin/Shinkei Shikkan Kenkyu Itakuhi ni yoru Kenkyu Hokokushu, Heisei 14 Nendo (2003-Jul), p. 590

Claims 1-19

The inventions in claims 1-19 appear to possess novelty and involve an inventive step based on the inventions described in documents 1-3.

Documents 1-3 do not describe or suggest an oligonucleotide wherein the third nucleotide from the 3' end consists of 2'-0, 4'-C-ethylene-bridged nucleic acid (ENA) and the other unit is a natural one.

Such an oligonucleotide could not be easily conceived of by a person skilled in the art.